

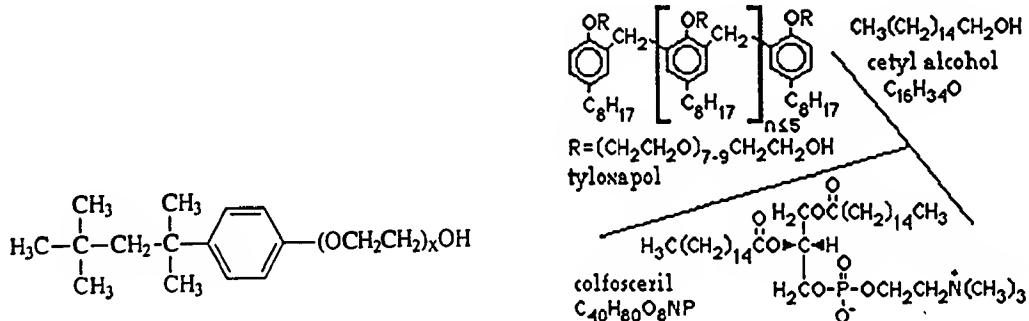
Examples of airway diseases that may be treated by the method of the present invention include cystic fibrosis, asthma, chronic obstructive pulmonary disease, bronchitis, and other airway diseases characterized by an inflammatory response. Antisense nucleotides to the A₁ and A₃ receptors are shown to be effective in the downregulation of A₁ or A₃ in the cell. One novel feature of this treatment, as compared to traditional treatments for adenosine-mediated bronchoconstriction, is that administration is direct to the lungs. Additionally, a receptor protein itself is reduced in amount, rather than merely interacting with a drug, and toxicity is reduced. Other proteins that may be targeted with antisense agents for the treatment of lung conditions include, but are not limited to: human A2a adenosine receptor, human A2b adenosine receptor, human IgE receptor β , human Fc-epsilon receptor CD23 antigen, human histidine decarboxylase, human beta tryptase, human tryptase-I, human prostaglandin D synthase, human cyclooxygenase-2, human eosinophil cationic protein, human eosinophil derived neurotoxin, human eosinophil peroxidase, human intercellular adhesion molecule-1 (ICAM-1), human vascular cell adhesion molecule-1 (VCAM-1), human endothelial leukocyte adhesion molecule-1 (ELAM-1), human P selectin, human endothelial monocyte activating factor, human IL-3, human IL-4, human IL-5, human IL-6, human IL-8, human monocyte-derived neutrophil chemotactic factor, human neutrophil elastase, human neutrophil oxidase factor, human cathepsin G, human defensin 1, human defensin 3, human macrophage inflammatory protein-1-alpha, human muscarinic acetylcholine receptor HM3, human fibronectin, human GM-CSF, human tumor necrosis factor α , human leukotriene C4 synthase, human major basic protein, and human endothelin 1. In these latter targets, and in target genes in general, it is particularly imperative to eliminate or reduce the adenosine content of the corresponding antisense oligonucleotide to prevent their breakdown products from liberating adenosine. --

Page 39, line 5 from the last, change "9941" into - 991) --.

Page 44, lines 6-7, delete "Brij 35, Triton X-100, and synthetic surfactants ALEC, Exosurf, Survan and Atovaquone", and substitute therefor -- polyoxy ethylene 23 lauryl ether (Brij 35[®]), t-octyl phenoxy polyethoxy ethanol (Triton X-100[®]), dipalmitoyl phosphatidyl choline (DPPC) and phosphatidyl glycerol (PG) (ALEC[®]), colfoceryl-cetyl alcohol-tyloxapol or colfosceril palmitate, cetyl alcohol and tyloxapol (Exosurf[®]),

phospholipids, neutral lipids, fatty acids and surfactant-associated proteins (Survanta®) and C₂₂H₁₉C₁₀ (Atovaquone®) --; and

after line 10, insert the following – The following chemical formulas are representative of the synthetic surfactants named below.



t-octyl phenoxy polyethoxy ethanol

Colfosceril-Cetyl Alcohol-Tyloxapol--.

Page 58, line 3 from the last, change "BUT" into –but--; and

before the last paragraph, insert the following:

Example 6: Additional Targets for Anti-sense Oligos in Accordance with the Invention

The method of the present invention is also practiced with the following antisense oligonucleotides targeted to their corresponding proteins, in essentially the same manner as given above, for the treatment of various conditions in the lungs:

Human A2a adenosine receptor: TGCTTTCTT TTCTGGGCCT C (SEQ ID NO:997)

Human A2b adenosine receptor: GGCGCCGTGC CGCGTCTTGG TGGCGGCGG (SEQ ID NO:998)

Human IgE receptor β: TTTCCCCTGG GTCTTCC (SEQ ID NO:999)

Human Fc-epsilon receptor CD23 antigen (IgE receptor): GCCTGTGTCT CTCCTCCT (SEQ ID NO:1000)

Human IgE receptor, " subunit: GCCTTTCTG GTTCTCTT (SEQ ID NO:1001)

Human IgE receptor, Fc epsilon R: GCCTGTGTCT GTCCTCCT (SEQ ID NO:1002)

Human histidine decarboxylase: TCTCCCTTGG GCTCTGGCTC CTTCTC (SEQ ID NO:1003)

Human beta tryptase: CTTGCTCCTG GGGGCCTCCT G (SEQ ID NO:1004)

Human tryptase-I: CTTGCTCCTG GGGGCCTCCT G (SEQ ID NO:1005)

Human prostaglandin D synthase: GCGCTCGGCC TGGTCCCGG (SEQ ID NO:1006)

Human cyclooxygenase-2: GGGCGCGGGC GAGCATCGC (SEQ ID NO:1007)

Human eosinophil cationic protein: CCTCCCTCCT GGTCTGTCTG C (SEQ ID NO:1008)

Human eosinophil derived neurotoxin: GCCCTGCTGC TCTTTCTGCT (SEQ ID NO:1009)

Human eosinophil peroxidase: GCGCTCGGCC TGGTCCCGG (SEQ ID NO:1010)

Human intercellular adhesion molecule-1 (CAM-1): GCGCGGGCCG GGGGCTGCTG GG (SEQ ID NO:1011)

Human vascular cell adhesion molecule 1 (VCAM-1): CCTCTTTCT GTTTTCCCC (SEQ ID NO:1012)

Human endothelial leukocyte adhesion molecule (ELAM-1): GTTCTGGCT TCTTCTGTC SEQ ID

NO:1013)

Human P Selectin: CTCTGCTGGT TTTCTGCCTT CTGCC (SEQ ID NO:1014)

Human endothelial monocyte activating factor: TTTTCTCTTT CGCTTTCTTT TCGTCTCCTG
TTCCTCCTTT T (SEQ ID NO:1015)

Human IL3: CTCTGTGTTG TTCTGGTCCT TCGTGGGGCT CTG(SEQ ID NO:1016)

Human IL4: CTCTGGTTGG CTTCCCTTC (SEQ ID NO:1017)

Human IL5: TCCCTGTTTC CCCCCCTTT (SEQ ID NO:1018)

Human IL6: GCTTCTCTTT CGTTCCCGGT GGGCTCG (SEQ ID NO:1019)

Human monocyte-derived neutrophil chemotactic factor: GCTTGTGTGC TCTGCTGTCT CT SEQ
ID NO:1020)

Human neutrophil elastase (medullasin): TGGTGGGGCT GGGGCTCCGG GGTCTCTGCC
CCTCCGTGC (SEQ ID NO:1021)

Human neutrophil oxidase factor: GTCTTCTTG TCCGCTGCC (SEQ ID NO:1022)

Human cathepsin G: GTGGGGCCTG CTCTCCCGGC CTCCG(SEQ ID NO:1023)

Human defensin 1: GGGTCCTCAT GGCTGGGG (SEQ ID NO:1024)

Human defensin 3: GGGTCCTCAT GGCTGGGGTC (SEQ ID NO:1025)

Human macrophage inflammatory protein-1-alpha: GTCTTGTCTT CTGGGCTCGT GCC (SEQ ID
NO:1026)

Human muscarinic acetylcholine receptor HM1: GTTCATGGTG GCTAGGTGGG GC (SEQ ID
NO:1027)

Human muscarinic acetylcholine receptor HM3: GGGGTGGTA GGCGTGTCT GGGG (SEQ ID
NO:1028)

Human fibronectin: CGGTTCCCTT TGCGGTC (SEQ ID NO:1029)

Human interleukin 8: GTGCTCCGGT GGCTTTTT (SEQ ID NO:1030)

Human GM-CSF: GGTCCAGCCA TGCGTCTGGG (SEQ ID NO:1031)

Human tumor necrosis factor ": GCTGGTCCTC TGCTGTCTT GCTG (SEQ ID NO:1032)

Human leukotriene C4 synthase: GCCCCGTCTG CTGCTCCTCG TGCCG (SEQ ID NO:1033)

Human major basic protein: GTTTCATCTT GGCTTTATCC (SEQ ID NO:1034)

Human Targets 997-1034: GATGGAGGGC GGCATGGCGG GGTGTTGGG CATCTGCCG
TGGGCCTAGC TCTCGCCTGC TTTTCTTTTC TGGGCCTCG CGCCGTGCCG CGTCTGGTG
GCGGCGGTTT CCCCTGGGTC TTCCGCCTGT GTCTCTCCTC CTGCCTTCTC TGTTCTCTT
GCCTGTGTCT GTCTCCCTTC TCCCTGGGC TCTGGCTCT TCTCCTTGCT CCTGGGGGCC
TCCCTGTTGC TCCTGGGGGC CTCCCTGCGCT CGGCCTGGTC CGGGGGGCCGC GGGCGAGCAT
CGCCCTCCTT CCTGGTCTGT CTGCGCCCTG CTGCTCTTC TGCTGCGCTC GGCCTGGTCC
CGGGCGCGGG CGGGGGGCTG CTGGGCCTCT TTCTGTCTT TCCCCTTCTT GGCTCTTCT
GTCTCTGCT CGTTTCTGC CTTCTGCCT TTCTCTTTC GCTTCTTTT CGTCTCTGT
TCCTCTTTT CTCTGTGTG TTCTGGTCCT TCGTGGGGCT CTGCTCTGGT TGGCTTCTT
CTCCCTGTTT CCCCCCTTTC TTCTCTTC GTTCCCGGTG GGCTCGGCTT GTGTGCTCTG
CTGTCTCTTG GTGGGGCTGG GGCTCCGGGTG TCTCTGCCCT TCCGTGCGTC CTTCTGTCC
GCTGCCGTGG GGCCTGCTCT CCCGGCCTCC GGGGTCTCA TGGCTGGGGG GGTCTCATG
GCTGGGGTCG TCTTGTCTT TGGGCTCGTG CGTTCATGG TGGCTAGGTG GGGCGGGGTG
GGTAGGCCGT TCTCGGTTTC CTTTGCCTGC GTGCTCCGGT GGCTTTTGG TCCAGCCATG
GGTCTGGGGC TGGTCCTCTG CTGTCCTTG TGCCCCCTGC TGCTGCTCCT CGTGCCGGTT
TCATCTGGC TTATCC (SEQ. ID NO:1035) --.

THE SEQUENCE LISTING

Please substitute the enclosed sequence listing section for the one filed November
15, 1999.